

Claims:

1. A method for genetically engineering a cell to regulate the expression of a target gene, the method comprising introducing into the cell a regulatably expressible nucleic acid encoding a fusion protein comprising a transcription regulatory domain and a composite DNA binding domain, wherein the composite DNA binding domain:
 - (a) binds to the target gene, and
 - (b) contains at least two nucleic acid-binding domains which:
 - (i) do not occur in the same protein in nature,
 - (ii) do not occur in the same protein in the order in which they are present in the composite DNA binding domain, or
 - (iii) do not occur in nature with the same spacing that is present in the composite DNA binding domain.
2. The method of claim 1 in which the composite DNA binding domain contains one or more zinc finger domains.
3. The method of claim 1 in which the cell is additionally engineered by the introduction thereto of a heterologous target gene linked to a nucleic acid sequence to which the fusion protein binds.
4. The method of claim 1 in which the target gene is an endogenous gene of the genetically engineered cell.
5. The method of claim 4 in which the target gene is linked to an endogenous nucleotide sequence to which the composite DNA binding domain of the fusion protein binds.
6. The method of any of claims 1 – 5 in which the transcription regulatory domain is a transcription activation domain.
7. The method of claim 6 wherein the transcription activation domain is a VP16 or p65 transcription activation domain.
8. The method of any of claims 1 – 5 in which the transcription regulatory domain is a transcription repression domain.
9. The method of any of claims 1 – 5 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.
10. The method of claim 6 in which regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.

11. The method of claim 7 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.

12. The method of claim 8 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.

13. The method of any of claims 1 – 5 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell in a host organism.

14. The method of claim 13 wherein the host organism is a mammal.

15. The method of claim 14 wherein the rodent is a mouse.

16. A method for regulating the expression of a target gene in a cell, the method comprising regulatably expressing a nucleic acid encoding a fusion protein comprising a transcription regulatory domain and a composite DNA binding domain, wherein the composite DNA binding domain:

- (a) binds to the target gene, and
- (b) contains at least two nucleic acid-binding domains which:
 - (i) do not occur in the same protein in nature,
 - (ii) do not occur in the same protein in the order in which they are present in the composite DNA binding domain, or
 - (iii) do not occur in nature with the same spacing that is present in the composite DNA binding domain.

17. The method of claim 16 in which the composite DNA binding domain contains one or more zinc finger domains.

18. The method of claim 16 in which the cell is additionally engineered by the introduction thereto of a heterologous target gene linked to a nucleic acid sequence to which the fusion protein binds.

19. The method of claim 16 in which the target gene is an endogenous gene of the genetically engineered cell.

20. The method of claim 19 in which the target gene is linked to an endogenous nucleotide sequence to which the composite DNA binding domain of the fusion protein binds.

21. The method of any of claims 16 - 20 in which the transcription regulatory domain is a transcription activation domain.

22. The method of claim 21 wherein the transcription activation domain is a VP16 or p65 transcription activation domain.

23. The method of any of claims 16 - 20 in which the transcription regulatory domain is a transcription repression domain.
24. The method of any of claims 16 - 20 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.
25. The method of claim 21 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.
26. The method of claim 22 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.
27. The method of claim 23 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell *ex vivo*.
28. The method of any of claims 16 - 20 in which the regulatably expressible nucleic acid encoding the fusion protein is introduced into the cell in a host organism.
29. The method of claim 28 wherein the host organism is a mammal.
30. The method of claim 29 wherein the rodent is a mouse.
31. A cell produced by the method of claim 1, and progeny thereof, containing a regulatably expressible nucleic acid encoding the fusion protein comprising a transcription regulatory domain and a composite DNA binding domain, wherein the fusion protein binds to a nucleic acid sequence linked to a target gene.
32. The cell of claim 31 in which the composite DNA binding domain contains one or more zinc finger domains.
33. The cell of claim 31 in which the target gene is a heterologous gene linked to a nucleic acid sequence to which the fusion protein binds.
34. The cell of claim 31 in which the target gene is an endogenous.
35. The cell of claim 34 in which the target gene is linked to an endogenous nucleotide sequence to which the composite DNA binding domain of the fusion protein binds.
36. The cell of any of claims 31 - 35 in which the transcription regulatory domain is a transcription activation domain.
37. The cell of claim 36 wherein the transcription activation domain is a VP16 or p65 transcription activation domain.
38. The cell of any of claims 31 - 35 in which the transcription regulatory domain is a transcription repression domain.
39. A non-human mammal containing the cell of any of claims 31 - 35.
40. A non-human mammal containing the cell of claim 36.
41. A non-human mammal containing the cell of claim 37.

42. A non-human mammal containing the cell of claim 38.
43. A mouse containing the cell of any of claims 31 – 35.
44. A mouse containing the cell of claim 36.
45. A mouse containing the cell of claim 37.
46. A mouse containing the cell of claim 38.

TOP SECRET